Validation of nonalcoholic fatty liver disease (NAFLD) related steatosis indices in metabolic associated fatty liver disease (MAFLD) and comparison of the diagnostic accuracy between NAFLD and MAFLD

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Background Metabolic-associated fatty liver disease (MAFLD) is a new term of nonalcoholic fatty liver disease (NAFLD), with newly proposed diagnostic criteria. The applicability of common noninvasive testing for screening NAFLD is unclear for the detection of MAFLD and requires reevaluation. We aimed to validate the effectiveness of traditional NAFLD-related steatosis indices for diagnosing MAFLD and to determine the optimal cutoff values as well as compare their accuracy between NAFLD and MAFLD diagnosis.

Methods This study enrolled 1866 participants from the National Health and Nutrition Examination Survey (NHANES) database (2017–2018). The diagnostic performances of fatty liver index (FLI), Framingham Steatosis Index (FSI), Zhejiang University index (ZJU), lipid accumulation product (LAP), hepatitis steatosis index (HSI) and visceral adiposity index (VAI) were evaluated using the area under the receiver operator characteristic (AUROC) curve and the optimal cutoff points were calculated according to maximum Youden's index.

Results FLI had the highest AUROC (0.840) for predicting MAFLD in the whole population, with a cutoff value of 56.93. The AUROCs of FLI, FSI, ZJU, LAP, HSI and VAI for predicting MAFLD/NAFLD were 0.840/0.812, 0.833/0.811, 0.826/0.811, 0.826/0.799, 0.814/0.803 and 0.747/0.729, respectively. The AUROC values of all indices decreased in the subgroup of the population with overweight or diabetes.

Conclusion The NAFLD-related scores would be equally useful to screen MAFLD and seemed to be more compatible with MAFLD. The FLI was optimal in both MAFLD and NAFLD diagnoses. However, a new predictive indicator suitable for various characteristics of the population is worth further development in the future. Eur J Gastroenterol Hepatol 35: 394–401

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a global public health issue, which shows an increasing prevalence with the growing epidemic of diabetes and obesity [1]. In 2020, an international expert consensus redefined NAFLD as metabolic-associated fatty liver disease (MAFLD), and updated diagnostic criteria were proposed [2]. MAFLD was diagnosed if there is evidence of hepatic steatosis by imaging, blood biomarkers/scores or histology, plus one of the three conditions: overweight/obesity or type 2 diabetes (T2DM) or the presence of metabolic risk abnormalities [2]. With changes in diet, lifestyle and health, MAFLD is expected to become the leading cause of chronic liver disease worldwide in the coming decades. In addition, MAFLD may progress and develop into cirrhosis and hepatocellular carcinoma. Therefore, the detection of MAFLD is crucial for public health research and the prevention of progress into advanced diseases for the individual.

Liver biopsy is the gold standard to diagnose fatty liver disease but invasiveness and unavoidable complications limit its clinical application. Abdominal ultrasonography is the recommended primary diagnostic tool for detecting hepatic steatosis of MAFLD [3]. However, for large-scale epidemiological investigations, it is difficult to perform ultrasonography on each participant due to its cost and the need for specialized equipment and staff. Steatosis indices, such as the fatty liver index (FLI) [4], Framingham Steatosis index (FSI) [5], Zhejiang University index (ZJU) [6], lipid accumulation product (LAP) [7], hepatitis steatosis index (HSI) [8] and visceral adiposity index (VAI) [9] have been tested and generally used in diagnosing

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Keywords: metabolic-associated fatty liver disease, National Health and Nutrition Examination Survey, noninvasive diagnosis, steatosis indices

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NAFLD [10]. MAFLD is the new term of NAFLD, with new diagnostic criteria that do not rule out significant alcohol consumption or any other liver diseases. Given the significant changes in diagnostic criteria between MAFLD and NAFLD, the utility of the common steatosis indices for identifying MAFLD is unclear and needs to be re-evaluated. The controlled attenuation parameter (CAP) is an accurate parameter to reflect liver steatosis detected by vibration-controlled transient elastography (VCTE) [11] and MAFLD has not been studied using VCTE and hepatic steatosis index. Because the National Health and Nutritional Examination Survey (NHANES) of the 2017–2018 cycle first performed VCTE in the US nationally representative sample, this study aimed to select the VCTE-diagnosed MAFLD group to examine the diagnostic capabilities of widely used NAFLD-related indices for diagnosing MAFLD and calculate the cutoff values as well as compare the diagnostic reliability and the cutoff values of the indices studied for MAFLD with those for NAFLD.

Materials and methods

Data source and study population

The NHANES is a continuous cross-sectional survey conducted by the National Center for Health Statistics (NCHS) for the assessment of health and nutritional status among the general public of the USA, which included unbiased demographics, dietary, examination, laboratory and questionnaire data. The NHANES has become a frequent database used to study MAFLD or NAFLD because of recently available data on FibroScan liver steatosis assessment [12–15]. The study cohort was obtained from the NHANES database (2017–2018). There were 9254 participants in NHANES 2017–2018 and the individuals were included in our study if he/she met the below criteria: (1) The fasting time before the venipuncture was at least 8 h; (2) Elastography examination status was described as complete [fasting >3 h; at least 10 valid measures; liver stiffness interquartile range/median E (IQRe) <30%]; (3) Complete records for the diagnosis of MAFLD and calculations of FLI, FSI, ZJU, LAP, HIS and VAI. The NHANES 2017–2018 survey was approved by the NCHS Ethics Review Board and informed consent was obtained from all participants. All NHANES datasets are anonymous and can be accessed online for free (https://www.cdc.gov/nchs/nhanes/index.htm).

Data collection and definitions

Data from interviews and physical examinations were collected for analysis, involving age, gender, ethnicity, waist circumference, BMI, SBP, DBP (SBP/DBP measured three times and the mean of the three measurements was adopted), alanine aminotransferase (ALT), aspartate aminotransferase (AST), high-density lipoprotein (HDL), triglyceride, gamma-glutamyl-transferase (GGT), fasting glucose, fasting insulin, hemoglobin A1c (HbA1c), high-sensitivity C-reactive protein (hs-CRP), markers of infection with hepatitis viruses, alcohol intake and the results of the liver ultrasound transient elastography. Detailed descriptions of the procedures and methodologies for measurements of the above data are reported elsewhere [16]. Homeostasis model assessment-estimated insulin resistance (HOMA-IR) was calculated as [fasting insulin (mU/ml) × fasting glucose (mmol/l)/22.5]. The markers of liver steatosis (FLI, FSI, ZJU, LAP, HIS and VAI) were calculated as Supplementary Table 1, Supplemental digital content 1, http://links.lww.com/EJGH/A810 and cutoff values of FLI, ZJU, LAP, HIS and VAI for detecting NAFLD were determined according to previous literature, with the cutoff points of 60 [4], 38 [6], 38 [17], 36 [8] and 1.78 [18], respectively.

Hypertension was identified if: (1) SBP value ≥140 mmHg and/or a DBP value ≥90 mmHg; (2) told by a doctor or other health professional and (3) current use of antihypertensive medications [19]. Diabetes was defined if: (1) told by a doctor or other health professional; (2) Use of antidiabetic medications; (3) HbA1c (%) >6.5; (4) fasting glucose (mmol/L) ≥7.0 mmol/L and (5) random blood glucose (mmol/L) ≥11.1 mmol/L [20]. MAFLD was diagnosed by the evidence of hepatic steatosis and at least one among the following: overweight/obesity, presence of T2DM and metabolic dysregulation [2]. Steatosis was defined as the median CAP ≥288 dB/m according to a recent study that compared CAP with MRI proton density fat fraction (MRI-PDFF) [21] and significant fibrosis was defined as the liver stiffness measurements ≥8 kPa [13]. We also used CAP scores of 288 with an IQR of CAP <30 dB/m to define steatosis for sensitivity analysis considering that the diagnostic accuracy of CAP for the detection of hepatic steatosis is more reliable when an IQR of CAP is <30 dB/m [21]. Overweight/obesity was defined as BMI ≥25 kg/m^2. Metabolic dysregulation was defined as the occurrence of two or more of the following conditions: (1) waist circumference ≥102 cm in males and 88 cm in females, (2) blood pressure ≥130/85 mmHg or treatment of specific drug, (3) triglyceride ≥1.70 mmol/L or treatment of specific drug, (4) HDL <1.0 mmol/L in men and <1.3 mmol/l in women, (5) prediabetes (i.e. fasting glucose: 5.6–6.9 mmol/l or 2-h post-load glucose: 7.8–11.0 mmol/l or HbA1c: 5.7–6.4%), (6) HOMA-IR ≥2.5 and (7) hs-CRP >2 mg/L.

We defined NAFLD as the presence of liver steatosis in the absence of other causes for steatosis (e.g. viral hepatitis and overdose of alcohol) [22]. Viral hepatitis was defined by the presence of HCV-RNA and/or confirmed hepatitis C antibodies (hepatitis C virus) or the hepatitis B surface antigen (hepatitis B virus) [15]. Overdose alcohol was indicated if >30 g/day for men and >20 g/day for women [15].

Statistical analysis

Continuous variables were expressed as median (interquartile range) and categorical variables were presented as counts (percentages, %). Mann-Whitney U-test was used for continuous variables and the χ^2 test for categorical variables. The area under the receiver operating characteristic (AUROC) curve was used to determine diagnostic performance and calculate the optimal cutoffs, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). The highest value of Youden's index was used to determine optimal cutoffs. Pairwise comparisons between AUROC values of different steatosis indices were conducted by the DeLong method. Statistical analyses were performed using SPSS version 22.0 and

MedCalc version 19.0.4 software. A two-tailed *P* value <0.05 was considered statistically significant.

Results

Characteristics of participants

After excluding unreliable elastographic examinations as well as missing data for diagnosis of MAFLD or NAFLD and calculations of steatosis indices, a total of 1866 participants from NHANES in the 2017–2018 cycle were included in our study (Fig. 1). Of these, 589 participants (280 female and 309 male) complied with diagnostic criteria of MAFLD and 535 participants (266 female and 269 male) was identified as NAFLD. As presented in Table 1, the prevalence of diabetes, hypertension and significant fibrosis in the MAFLD/NAFLD group were significantly higher than non-MAFLD/non-NAFLD group. The participants with MAFLD or NAFLD have higher waist circumference, BMI, SBP, DBP, ALT, AST, triglyceride, GGT and lower HDL than those of the control group. The values of all steatosis indices were significantly higher in people with MAFLD/NAFLD than without MAFLD/NAFLD. The characteristics of the 705 subjects with IQR of CAP <30 dB/m for analysis of sensitivity were shown in Supplementary Table 2, Supplemental digital content 2, http://links.lww.com/EJGH/A811.

Comparisons between index systems for MAFLD and NAFLD prediction

The AUROC values of steatosis indices for the prediction of MAFLD and NAFLD were calculated and pairwise comparisons between indices were performed. The predicted indices showed adequate diagnostic performance in detecting MAFLD, with AUROC values over 0.800 except for VAI had an acceptable performance with AUROC of 0.747. The results of pairwise comparisons of different indices were listed in Table 2. The FLI had the highest AUROC of 0.840 [95% confidence interval (CI), 0.822–0.858], followed by the FSI (0.833; 95% CI, 0.815–0.852), ZJU (0.826; 95% CI, 0.808–0.845), LAP (0.826; 95% CI, 0.807–0.844), HSI (0.814; 95% CI, 0.795–0.834) and VAI (0.747; 95% CI, 0.723–0.770) (Fig. 2 and Table 3).

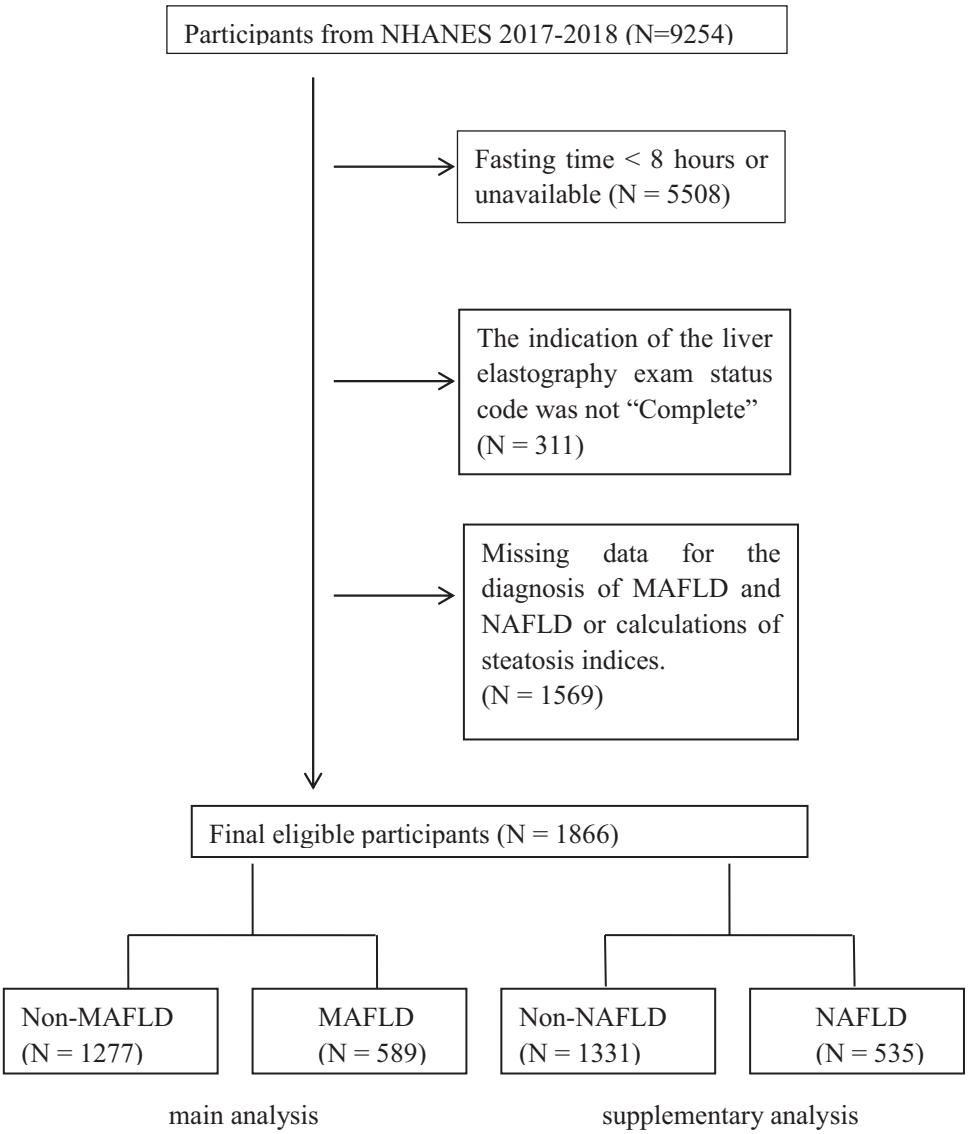

Fig. 1. Flowchart of the enrolled participants in the study.

Table 1. Characteristics of the subjects according to MAFLD or NAFLD

Characteristics	Non-MAFLD ($n=1277$)	MAFLD ($n=589$)	*P* value	Non-NAFLD ($n=1331$)	NAFLD ($n=535$)	*P* value
Age (year)	40.00 (23.00–60.00)	54.00 (39.00–64.00)	<0.001	41.00 (23.00–60.00)	54.00 (38.00–64.00)	<0.001
Female (N, %)	692, 54.2%	280, 47.5%	0.008	706, 53.0%	266, 49.7%	0.194
Race (N, %)			<0.001			<0.001
Mexican American	148, 11.6%	126, 21.4%		161, 12.1%	113, 21.1%	
Other Hispanic	114, 8.9%	54, 9.2%		121, 9.1%	47, 8.8%	
Non-Hispanic	759, 59.4%	326, 55.3%		789, 59.3%	296, 55.3%	
Other Race	256, 20.0%	83, 14.1%		260, 19.5%	79, 14.8%	
Diabetes (N, %)	139, 10.9%	210, 35.7%	<0.001	156, 11.7%	193, 36.1%	<0.001
Hypertension (N, %)	394, 30.9%	324, 55.0%	<0.001	427, 32.1%	291, 54.4%	<0.001
Significant fibrosis (N, %)	62, 4.9%	99, 16.8%	<0.001	71, 5.3%	90, 16.8%	<0.001
Waist circumference (cm)	90.30 (80.40–101.50)	109.80 (99.80–119.80)	<0.001	91.70 (80.80–102.50)	109.80 (99.80–120.10)	<0.001
BMI (kg/m2)	25.80 (22.40–29.90)	32.50 (28.80–37.00)	<0.001	26.00 (22.60–30.20)	32.40 (28.85–37.25)	<0.001
SBP (mmHg)	115.0 (107.0–129.0)	126.0 (116.0–139.0)	<0.001	116.0 (108.0–130.0)	125.0 (115.0–138.0)	<0.001
DBP (mmHg)	69.00 (63.00–77.00)	74.00 (66.00–81.00)	<0.001	70.00 (63.00–77.00)	74.00 (65.00–81.00)	<0.001
ALT (U/L)	15.00 (11.00–22.00)	22.00 (16.00–33.00)	<0.001	16.00 (11.00–22.00)	21.00 (15.00–32.00)	<0.001
AST (U/L)	18.00 (15.00–22.00)	20.00 (16.00–27.00)	<0.001	19.00 (15.00–23.00)	20.00 (16.00–26.00)	<0.001
HDL (mmol/L)	1.40 (1.16–1.66)	1.19 (1.03–1.40)	<0.001	1.40 (1.16–1.66)	1.19 (1.03–1.40)	<0.001
TG (mmol/L)	0.82 (0.58–1.23)	1.32 (0.96–1.86)	<0.001	0.85 (0.59–1.29)	1.30 (0.93–1.85)	<0.001
GGT (U/L)	17.00 (12.00–25.00)	25.00 (18.00–40.00)	<0.001	18.00 (12.00–27.00)	24.00 (17.00–38.00)	<0.001
Fasting glucose (mmol/l)	5.55 (5.27–5.94)	6.11 (5.61–7.11)	<0.001	5.55 (5.27–6.00)	6.11 (5.61–7.11)	<0.001
Fasting insulin (mU/ml)	8.25 (5.63–12.32)	15.74 (10.09–24.12)	<0.001	8.40 (5.79–12.74)	15.74 (10.16–24.52)	<0.001
HbA1c	5.40 (5.20–5.70)	5.80 (5.40–6.40)	<0.001	5.40 (5.20–5.70)	5.80 (5.40–6.40)	<0.001
hs-CRP (mg/L)	1.27 (0.59–2.96)	2.94 (1.33–5.86)	<0.001	1.29 (0.60–2.99)	2.99 (1.35–6.00)	<0.001
HOMA-IR	2.07 (1.39–3.27)	4.63 (2.81–7.46)	<0.001	2.12 (1.42–3.38)	4.68 (2.82–7.55)	<0.001
FLI	26.20 (7.41–59.93)	83.88 (59.57–94.84)	<0.001	29.49 (8.19–63.64)	83.43 (58.43–94.82)	<0.001
FSI	10.10 (3.88–24.69)	44.72 (23.86–70.44)	<0.001	11.09 (4.08–26.57)	44.37 (23.37–70.42)	<0.001
ZJU	36.10 (32.15–41.31)	45.35 (40.97–50.87)	<0.001	36.45 (32.35–41.75)	45.47 (40.92–50.94)	<0.001
LAP	24.04 (12.11–43.69)	63.71 (42.30–94.95)	<0.001	25.46 (12.66–46.15)	62.05 (40.32–94.82)	<0.001
HSI	34.00 (30.00–39.47)	43.61 (38.74–48.87)	<0.001	34.47 (30.20–39.85)	43.71 (38.79–49.02)	<0.001
VAI	0.97 (0.60–1.54)	1.92 (1.21–2.86)	<0.001	0.99 (0.62–1.60)	1.88 (1.16–2.86)	<0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FLI, fatty liver index; FSI, Framingham Steatosis Index; GGT, gamma-glutamyl-transferase; HbA1c, Hemoglobin A1c; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; HSI, hepatitis steatosis index; LAP, lipid accumulation product; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; TG, triglyceride; VAI, visceral adiposity index; ZJU, Zhejiang University index.

The cut-off value of FLI was 56.93 for the diagnosis of MAFLD, with a sensitivity of 0.783, a specificity of 0.732, a PPV of 0.574, and an NPV of 0.880 (Table 3). The AUROCs of studied tools in detecting NAFLD were above 0.800 besides VAI but slightly lower than those of MAFLD, with the values of 0.812 (95% CI, 0.792–0.832) for FLI, 0.811 (95% CI, 0.791–0.832) for FSI, 0.811 (95% CI, 0.791–0.831) for ZJU, 0.799 (95% CI, 0.778–0.820) for LAP, 0.803 (95% CI, 0.782–0.823) for HSI and 0.729 (95% CI, 0.705–0.754) for VAI, respectively (Fig. 3 and Table 3). The FLI still had the highest AUROC value of 0.812 for screening NAFLD, with a sensitivity of 0.727, a specificity of 0.724 and an NPV of 0.868 when applying the cut-off point of 60 (Table 3). The sensitivity analysis showed similar results (Supplementary Table 3, Supplemental digital content 3, http://links.lww.com/EJGH/A812 and Supplementary Table 4, Supplemental digital content 4, http://links.lww.com/EJGH/A813).

Diagnostic accuracy of indices for diagnosing MAFLD in different subgroups.

Subgroup analysis was conducted by dividing the participants into different groups according to age, gender, BMI and the presence of diabetes. The FLI showed better diagnostic ability in different subgroups than other steatosis indices except for the male group. In the male group, the AUROC of FLI was 0.845, which was slightly lower than FSI (AUROC, 0.849) and ZJU (AUROC, 0.846). The AUROC values of all indices for diagnosing MAFLD

Table 2. Pairwise comparisons of receiver operatingcharacteristic curves of different steatosis indices

Indices	FLI	FSI	ZJU	LAP	HSI	VAI
Accuracy for MAFLD diagnosis						
AUROC	0.840	0.833	0.826	0.826	0.814	0.747
(95% CI)	(0.822–0.858)	(0.815–0.852)	(0.808–0.845)	(0.807–0.844)	(0.795–0.834)	(0.723–0.770)
FLI	–	–	–	–	–	–
FSI	$P=0.122$	–	–	–	–	–
ZJU	$P=0.008$	$P=0.196$	–	–	–	–
LAP	$P=0.026$	$P=0.272$	$P=0.937$	–	–	–
HSI	$P<0.001$	$P<0.112$	$P<0.001$	$P=0.253$	–	–
VAI	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$	–
Accuracy for NAFLD diagnosis						
AUROC	0.812	0.811	0.811	0.799	0.803	0.729
(95% CI)	(0.792–0.832)	(0.791–0.832)	(0.791–0.831)	(0.778–0.820)	(0.782–0.823)	(0.705–0.754)
FLI	–	–	–	–	–	–
FSI	$P=0.889$	–	–	–	–	–
ZJU	$P=0.836$	$P=0.935$	–	–	–	–
LAP	$P=0.052$	$P=0.087$	$P=0.179$	–	–	–
HSI	$P=0.129$	$P=0.165$	$P=0.014$	$P=0.714$	–	–
VAI	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$	–

Endash indicates repeated comparisons.
AUROC, area under the receiver operating characteristic; CI, confidence interval; FLI, fatty liver index; FSI, Framingham Steatosis Index; HSI, hepatitis steatosis index; LAP, lipid accumulation product; MAFLD, metabolic dysfunction-associated fatty liver disease; NAFLD, nonalcoholic fatty liver disease; VAI, visceral adiposity index; ZJU, Zhejiang University index.

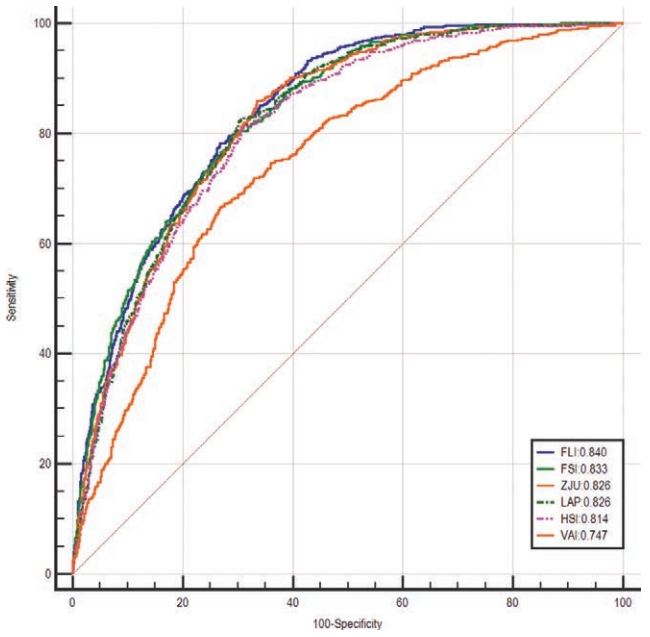

Fig. 2. Receiver operating characteristic curves of FLI, FSI, ZJU, LAP, HSI, and VAI for screening MAFLD. FLI, fatty liver index; FSI, Framingham Steatosis Index; HSI, hepatitis steatosis index; LAP, lipid accumulation product; MAFLD, metabolic dysfunction-associated fatty liver disease; VAI, visceral adiposity index; ZJU, Zhejiang University index.

tended to decrease in those having diabetes and BMI over 25 compared with those in the other subgroups. Table 4 showed the diagnostic performance and population-specific cut-off values of these indices in different subgroups.

Discussion

Liver biopsy or imaging used to diagnose MAFLD is burdensome and hard to implement on a large scale, so applying noninvasive algorithms is a valuable alternative method. This study for the first time validated the NAFLD-related steatosis indices for screening VCTE-diagnosed MAFLD and compared the diagnostic validity of noninvasive clinical scores between NAFLD and MAFLD. FLI, FSI, ZJU, LAP and HSI showed satisfactory performance in the whole and subgroups in detecting MAFLD whereas the AUROC of VAI varied greatly in the different subgroups. The FLI had the highest AUROC in the general US population with a sensitivity of 0.783 and a specificity of 0.732. The cut-off value of FLI was 56.93. In subgroup analysis, the diagnostic accuracy of all indices declined in people with high BMI (BMI ≥25) or diabetes. Furthermore, our findings suggested the diagnostic capacity of NAFLD-related indices had not been compromised by MAFLD nomenclature whereas all the scores appear to be more compatible with MAFLD with few differences between the cutoff points. The FLI outperformed other scores in both diagnoses of MAFLD and NAFLD in the general population.

NAFLD has been redefined as MAFLD, which is no longer an exclusion diagnosis. In addition, the accuracy of indices is influenced by the age, sex, ethnicity and region of the sample populations. Therefore, further validation of the indices widely used in NAFLD diagnosis is required for different cohorts to distinguish between people with MAFLD and those without. So far, only a few studies examined the validity of the steatosis index in discriminating MAFLD. A comparison of the performance of hepatic steatosis indices in identifying MAFLD was conducted by Han and Lee [23] based on the Korean population. Although ethnicity and environment are different from Europe, their findings were similar to those of our study showing FLI performs better at diagnosing MAFLD. It is worth noting that FLI has been recommended for diagnosing fatty liver in large population studies by guidelines [3]. The predictive ability of the FSI for MAFLD has not been validated and the prediction power of ZJU, an algorithm developed in China, is unclear in western populations although it showed clinically acceptable capability for the detection of MAFLD in eastern populations [23]. Our study observed that FSI and ZJU had similar diagnostic performances as FLI and their AUROC values in the male group were slightly higher than FLI. Unfortunately, they contain more parameters and their calculations are more

Table 3. Diagnostic performances of different steatosis indices

Index systems	AUROC	SEN	SPE	PPV	NPV	Cut-off value
Diagnostic ability for MAFLD						
FLI	0.840 (0.822–0.858)	0.783	0.732	0.574	0.880	56.93
FSI	0.833 (0.815–0.852)	0.793	0.710	0.558	0.881	21.12
ZJU	0.826 (0.808–0.845)	0.859	0.665	0.542	0.911	39.16
LAP	0.826 (0.807–0.844)	0.827	0.694	0.555	0.897	36.74
HSI	0.814 (0.795–0.834)	0.810	0.691	0.547	0.887	37.85
VAI	0.747 (0.723–0.770)	0.666	0.731	0.533	0.826	1.47
Diagnostic ability for NAFLD						
FLI	0.812 (0.792–0.832)	0.727	0.724	0.515	0.868	60.00
FSI	0.811 (0.791–0.832)	0.753	0.708	0.509	0.877	23.00
ZJU	0.811 (0.791–0.831)	0.892	0.583	0.462	0.930	38.00
LAP	0.799 (0.778–0.820)	0.787	0.678	0.495	0.888	38.00
HSI	0.803 (0.782–0.823)	0.877	0.571	0.451	0.920	36.00
VAI	0.729 (0.705–0.754)	0.533	0.787	0.501	0.807	1.78

AUROC, area under the receiver operating characteristic; FLI, fatty liver index; FSI, Framingham Steatosis Index; HSI, hepatitis steatosis index; LAP, lipid accumulation product; NAFLD, nonalcoholic fatty liver disease; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; SEN, sensitivity; SPE, specificity; VAI, visceral adiposity index; ZJU, Zhejiang University index.

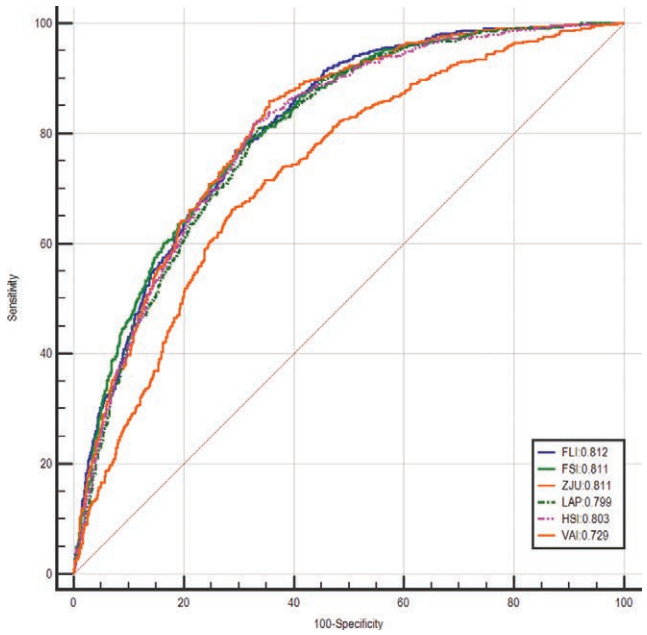

Fig. 3. Receiver operating characteristic curves of FLI, FSI, ZJU, LAP, HSI, and VAI for screening NAFLD. FLI, fatty liver index; FSI, Framingham Steatosis Index; HSI, hepatitis steatosis index; LAP, lipid accumulation product; NAFLD, nonalcoholic fatty liver disease; VAI, visceral adiposity index; ZJU, Zhejiang University index.

complex than FLI [5,6]. LAP, a cost-effective index only based on waist circumference and triglyceride [7], is a good choice for screening MAFLD when FLI is unavailable, especially in the normal BMI US population (BMI <25) as its AUROC value is second only to FLI in the normal-weight subgroup. HSI was developed based on ALT/AST ratio and BMI [8] and is simpler than FLI but it is not as well as FLI. Some studies have validated VAI for the prediction of MAFLD while its predictive role requires further determination [24]. The VAI had a variable accuracy among subgroups and relatively unsatisfactory diagnostic value in the whole population compared to other scores according to our findings.

These noninvasive clinical scores have shown useful diagnostic value in NAFLD. In the original studies, the AUROC values of FLI, FSI, ZJU and HSI for identifying steatosis were 0.840, 0.845, 0.822 and 0.812, respectively, with cutoff values of 60, 23, 38 and 36, respectively [4–6,8]. Although LAP and VAI were developed for predicting cardiovascular disease, previous studies have demonstrated that the discriminative capacity of these steatosis scores for NAFLD could reach 75%, with the cutoff points of 38 for LAP and 1.78 for VAI based on biopsy-proven NAFLD [17,18]. One study in Italy reported FLI (0.77), ZJU (0.76), HSI (0.75) and LAP (0.74) in the diagnosis of NAFLD [25], another study from China showed promising results of FLI (0.880), FSI (0.864), ZJU (0.861), LAP (0.853) and HSI (0.833) for identifying NAFLD [26]. To compare the diagnostic reliability and the cutoff values of the indices between NAFLD and MAFLD, we validated these indices again in our cross-sectional cohort, and our results showing they are reliable predictors for NAFLD were consistent with the available evidence. Moreover, the performances of the studied noninvasive scores in MAFLD are as good as previously reported for NAFLD and the optimal cutoff points for predicting MAFLD were 56.93 (FLI), 21.12 (FSI), 39.16 (ZJU), 36.74 (LAP), 37.85 (HSI) and 1.47 (LAP), respectively, which was similar with those previously reported cutoff points of 60 (FLI), 23 (FSI), ZJU (38) HSI (36) and VAI (1.78) for NAFLD. FLI performs best both in diagnosing MAFLD and NAFLD. These data support the notion that a name change from NAFLD to MAFLD seems not to influence the diagnostic accuracy for NAFLD-related steatosis indices. Furthermore, according to the results showing AUROC values for all indices were somewhat higher in MAFLD than in NAFLD of this study, NAFLD-related steatosis indices seem to be more compatible with MAFLD. The MAFLD diagnostic criteria include waist circumference, BMI, triglyceride, HDL and fasting glucose, which are parameters in steatosis indices, so this may explain why indices predict MAFLD well.

Recently, another study investigated the diagnostic accuracy of common hepatic steatosis formulas for MAFLD based on the NHANES database from 1988 to 1994 [27]. However, as the authors admitted in their original literature, the diagnosis of hepatic steatosis was based on ultrasonography rather than CAP measurement by VCTE, a more sensitive method for assessing steatosis. On the other hand, considering the prevalence of MAFLD has gradually risen with the growing incidence of obesity and T2DM in these years according to a recent study

Table 4. Diagnostic performance of different indices for diagnosing MAFLD in different subgroups

Indices	ROC (95% CI)	SEN	SPE	PPV	NPV	Cut-off value
Age <60						
FLI	0.858 (0.837–0.878)	0.892	0.672	0.510	0.942	41.50
FSI	0.853 (0.832–0.874)	0.775	0.770	0.564	0.899	21.25
ZJU	0.843 (0.822–0.865)	0.917	0.636	0.492	0.952	37.97
LAP	0.845 (0.823–0.867)	0.806	0.754	0.557	0.910	36.72
HSI	0.832 (0.810–0.855)	0.836	0.691	0.509	0.917	37.74
VAI	0.767 (0.739–0.795)	0.669	0.768	0.525	0.858	1.47
Age ≥60						
FLI	0.791 (0.754–0.827)	0.777	0.658	0.605	0.814	58.04
FSI	0.777 (0.739–0.815)	0.677	0.770	0.665	0.779	32.47
ZJU	0.783 (0.746–0.821)	0.856	0.593	0.587	0.859	39.14
LAP	0.768 (0.730–0.807)	0.677	0.729	0.628	0.769	51.00
HSI	0.778 (0.740–0.817)	0.782	0.676	0.620	0.821	37.88
VAI	0.690 (0.646–0.733)	0.616	0.699	0.580	0.729	1.61
Male						
FLI	0.845 (0.820–0.870)	0.812	0.721	0.606	0.879	56.93
FSI	0.849 (0.824–0.875)	0.783	0.754	0.627	0.868	24.18
ZJU	0.846 (0.820–0.872)	0.812	0.744	0.626	0.882	39.16
LAP	0.832 (0.805–0.858)	0.806	0.718	0.601	0.875	37.31
HSI	0.828 (0.800–0.855)	0.793	0.718	0.598	0.868	37.19
VAI	0.753 (0.721–0.786)	0.641	0.769	0.595	0.802	1.45
Female						
FLI	0.835 (0.810–0.860)	0.925	0.604	0.486	0.952	35.74
FSI	0.818 (0.791–0.845)	0.771	0.710	0.518	0.885	21.12
ZJU	0.824 (0.798–0.850)	0.904	0.607	0.482	0.940	39.36
LAP	0.822 (0.796–0.848)	0.843	0.682	0.518	0.915	36.72
HSI	0.814 (0.788–0.841)	0.868	0.640	0.494	0.923	37.84
VAI	0.749 (0.716–0.782)	0.768	0.632	0.457	0.871	1.29
BMI <25						
FLI	0.870 (0.810–0.931)	0.781	0.840	0.216	0.986	19.82
FSI	0.837 (0.768–0.905)	0.844	0.714	0.142	0.988	5.69
ZJU	0.827 (0.743–0.911)	0.656	0.911	0.292	0.979	35.33
LAP	0.861 (0.788–0.934)	0.875	0.781	0.183	0.991	22.68
HSI	0.757 (0.667–0.846)	0.750	0.730	0.135	0.981	31.37
VAI	0.824 (0.735–0.912)	0.844	0.761	0.166	0.989	1.19
BMI ≥25						
FLI	0.752 (0.725–0.778)	0.702	0.675	0.630	0.742	69.12
FSI	0.743 (0.716–0.770)	0.632	0.741	0.658	0.719	35.75
ZJU	0.728 (0.700–0.756)	0.664	0.683	0.623	0.721	43.24
LAP	0.738 (0.710–0.765)	0.724	0.638	0.612	0.745	46.12
HSI	0.716 (0.688–0.744)	0.671	0.656	0.606	0.717	41.06
VAI	0.679 (0.649–0.708)	0.670	0.634	0.590	0.709	1.45
Diabetes						
FLI	0.736 (0.683–0.790)	0.524	0.827	0.821	0.535	88.23
FSI	0.736 (0.682–0.789)	0.719	0.655	0.759	0.607	36.48
ZJU	0.739 (0.686–0.792)	0.690	0.676	0.763	0.591	44.55
LAP	0.724 (0.669–0.778)	0.600	0.748	0.783	0.553	69.57
HSI	0.719 (0.663–0.774)	0.881	0.460	0.712	0.719	38.08
VAI	0.658 (0.600–0.717)	0.729	0.561	0.715	0.578	1.63
No diabetes						
FLI	0.841 (0.820–0.862)	0.908	0.609	0.436	0.952	35.19
FSI	0.829 (0.807–0.851)	0.747	0.748	0.496	0.897	21.12
ZJU	0.820 (0.797–0.842)	0.807	0.708	0.480	0.917	39.17
LAP	0.824 (0.802–0.846)	0.792	0.731	0.495	0.913	36.74
HSI	0.812 (0.788–0.835)	0.768	0.721	0.479	0.903	37.85
VAI	0.727 (0.709–0.765)	0.704	0.670	0.416	0.872	1.22

FLI, fatty liver index; FSI, Framingham Steatosis Index; HSI, hepatitis steatosis index; LAP, lipid accumulation product; NAFLD, nonalcoholic fatty liver disease; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; SEN, sensitivity; SPE, specificity; VAI, visceral adiposity index; ZJU, Zhejiang University index.

based on the NHANES database [13], it seems reasonable to reconsider the accuracy of traditional steatosis indices in differentiating MAFLD among current US population. Interestingly, in this study, all fatty liver formulae had declined AUROC values in the subgroup with high BMI (≥25 kg/m^2) rather than low BMI (<25 kg/m^2). Our findings were contrary, which is probably explained by the rising prevalence of obesity as the result of socioeconomic changes and the rapid shift from malnutrition to over-calorie eating habits. Besides overweight people, the performance of these scores was poor in people with diabetes. Moreover, the cutoff values varied significantly in different subgroups. Thus, a novel efficient index that is suitable for all populations is required for the detection of MAFLD patients, with population-specific cutoff values.

We have to acknowledge some limitations in our study. On the one hand, the evidence of hepatic steatosis was assessed by VCTE rather than a liver biopsy. However, CAP using transient elastography is regarded as a reliable method to diagnose liver steatosis according to previous literature [28,29] and biopsy is not easy to perform in clinical settings. On the other hand, the data used in the study consisted mainly of Caucasians in the USA and the performance of steatosis indices in other cohorts

remains unclear. More studies in more regions and races are required to explore the accuracy of indices.

In conclusion, the FLI, FSI, ZJU, LAP, HIS and VAI as frequently used in NAFLD were still useful in identifying VCTE-diagnosed MAFLD and even seem to improve MAFLD. The FLI performed best in the whole population, calculated by serum biomarkers, and may serve as a practical and alternative tool to screen MAFLD when imaging modalities, such as in large-scale epidemiological studies, are not available or feasible. A new prediction model considering all kinds of characteristics of the population is hoped to be developed in the future.

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M.D. and G.L. conceived and designed the study. J.C. and X.M. performed the analysis. J.C., X.M. and G.L. wrote and reviewed the article.

Conflicts of interest

There are no conflicts of interest.

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